UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,015	02/17/2005	Noboru Yamaji	Q86324	5025

65565 7590 01/27/2009

SUGHRUE-265550
2100 PENNSYLVANIA AVE. NW
WASHINGTON, DC 20037-3213

EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
01/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,015	YAMAJI ET AL.	
	Examiner	Art Unit	
	ANDREW D. KOSAR	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Appeal Brief filed October 27, 2008 appealing from the Office action mailed April 8, 2008 is acknowledged and has been fully considered. Upon further consideration and review, new grounds of rejection are required. The finality of the Office Action mailed April 8, 2008 is withdrawn.

Information Disclosure Statement

It is noted that Applicant's Appeal Brief indicates certain evidence was submitted and entered by the examiner. Respectfully, the references were not cited on a proper IDS, and thus are not evidence that was 'entered'. Should Applicant wish to have the references properly considered, they should be cited on an IDS. Further, the 'partial translations' should be provided with the complete reference, or portion thereof, and a complete citation. Additionally, it should be noted that 'evidence' includes citation of the reference cited in the rejection.

Specification and Claim Objections

The specification and Claim 19 are objected to because of the following informalities: The specification and claim 19 recite various HDAC inhibitors by their 'common' name, e.g. CHAP, FK228, etc., however the compounds are not defined in the specification, or in the claim. The chemical name should be placed in the claim and specification at the first occurence. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18-21 are rejected under 35 U.S.C. 102(e) as being anticipated by CHUNG (US 2005/0245439 A1).

The instant claims are generally drawn to treating osteoarthritis with a histone deacetylase inhibitor.

Chung teaches preventing joint destruction in a joint or musculoskeletal disease comprising administering a therapeutically effective amount of an HDACi (e.g. claim 1), where the HDACi is a hydroxamic acid derivative, a short chain fatty acid (SCFA), a cyclic tetrapeptide, a benzamide derivative, or an electrophilic ketone derivative (e.g. claim 2), where the hydroxamic acid derivative is selected from suberoylanilide hydroxamic acid (SAHA), pyroxamide, M-carboxycinnamic acid bishydroxamide (CBHA), trichostatin A (TSA), trichostatin C, salicylihydroxamic acid (SBHA), azelaic bishydroxamic acid (ABHA), azelaic-1-hydroxamate-9-anilide (AAHA), 6-(3-chlorophenylureido) carpoic hydroxamic acid (3Cl-UCHA), oxamflatin, A-161906, scriptaid, PXD-101, LAQ-824, cyclic hydroxamic acid-containing peptide(CHAP), MW2796, and MW2996 (e.g. claim 3); where the cyclic tetrapeptide is selected from trapoxin A, FR901228 (FK 228 or Depsipeptide), FR225497, apicidin, CHAP,

HC-toxin, WF27082, and chlamydocin (claim 4); where the short chain fatty acid is selected from sodium butyrate, isovalerate, valerate, 4-phenylbutyrate (4-PBA), 4-phenylbutyrate sodium (PBS), arginine butyrate, propionate, butyramide, isobutyramide, phenylacetate, 3-bromopropionate, tributyrin, valproic acid, and valproate; wherein the benzamide derivative is selected from a group consisting of CI-994, MS-27-275 (MS-275), and a 3'-amino derivative of MS-27-275 (e.g. claim 6); where the electrophilic ketone derivative is a trifluoromethyl ketone or an alpha-keto amide (claim 7); or the HDACi is Depudecin (claim 8).

Chung teaches that the joint disease is selected from a group consisting of bone loss, bone fractures, osteonecrosis, osteoporosis, osteopenia, glucocorticoid induced osteoporosis, Paget's disease, Gaucher's disease, sickle cell anemia, osteomyelitis, abnormally increased bone turnover, osteoclasis, periodontal disease, periprosthetic osteolysis, degenerative joint disease, osteoarthritis, gouty arthritis, septic arthritis, and osteogenesis imperfecta (e.g. claim 14). Because there are so few members of the group of joint diseases in the claim, one could as once envisage each and every disease separately, including osteoarthritis. It is noted that osteoarthritis and "degenerative joint disease" are the same condition.

Claims 18-21 are rejected under 35 U.S.C. 102(e) as being anticipated by WATKINS (WO 02/30879 A2).

The instant claims are drawn generally to administering an HDACi to treat osteoarthritis.

Watkins teaches that HDACi (histone deacetylase inhibitor(s)) are well known for treating osteoarthritis (e.g. page 111, lines 1 and 2) and teaches a myriad of HDACi, including those instantly claimed (e.g. trichostatin A and SAHA, page 4, page 111). When looking at the

disclosure of Watkins the artisan would be aware that if a compound is used to treat a condition, one would use a therapeutically effective dose, otherwise it would fail to treat the condition.

Further, it is noted that the instant disclosure (page 6, 2nd full paragraph) states that HDAC inhibitors have been used for RA and osteoarthritis ("Additionally, in the patent specification (Patent Reference 1) for the FK228 reduced form, a number of diseases are cited for the reason that the FK228 reduced form is effective for diseases induced by abnormal gene expression by its HDAC-inhibitory activity. Therein, although rheumatic arthritis and osteoarthritis are cited, any specific effect is not described and the basis which indicates a therapeutic effect is not shown.").

Applicant argue that Watkins "does not contain an enabling disclosure of the treatment of osteoarthritis; and therefore the present invention is not anticipated." (VII. Argument, page 8). To further this position, Applicant further argues that Watkins does not "teach a specific working example where an HDAC inhibitor is administered to a subject actually having osteoarthritis." (page 8). Applicant states "At page 110-111, Watkins, et al. states that inflammatory diseases such as osteoarthritis and rheumatoid arthritis are conditions which are known to be treated by HDAC inhibitors. However, this statement is contrary to the knowledge and skill in the art with respect to treatment of osteoarthritis and cannot serve as an enabling disclosure." (page 9). Further stating that specifically, at pages 110-111, "Watkins discloses:

> The compounds of the present invention may also be used in the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A). Examples of such conditions include, but are not limited to the following:
>
> Cancer (see, e.g., Vigushin et al., 2001).

> Inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996)."

Applicant further asserts that Watkins is not enabling, by attacking the references Dangond and Takahasi. Applicant asserts that neither Dangond or Takahasi discuss osteoarthritis, and are directed to immunosupression and inhibition of proliferation and allegedly "fails to establish a nexus between HDACs and osteoarthritis." (page 10).

Applicant summarizes the arguments by stating, "In this case, Appellants have pointed out that: (1) Watkins does not provide a specific example wherein an HDAC inhibitor is used to treat osteoarthritis and does not provide an enabling disclosure for such a method of treatment; (2) the references referred to by Watkins in support of the statement that the method of treatment of osteoarthritis using HDACi's was well known do not even mention these conditions and thus do not support the assertion made by Watkins; (3) none of the other references of record indicate that osteoarthritis is "known to be mediated by HDAC" or "known to be treated by HDAC inhibitors"; and (4) the Examiner has not pointed to any other references in support of his position that Watkins is enabling for the treatment of osteoarthritis. On the other hand, the Examiner has made statements regarding the disclosure of Watkins which are contradicted by objective evidence of the knowledge and skill available in the art. Accordingly, the evidence presented by Appellants is more convincing than the mere statements of the Examiner. Thus, patentability of the present claims is supported by a preponderance of the evidence when the totality of the record is properly taken into consideration." (spanning pages 13 and 14).

Applicant's arguments have been fully considered. Respectfully, the examiner disagrees.

It should be noted that the rejection set forth is based upon Watkins, and not in view of Takahashi or Dangond. Additionally, there is no express or implicit statement of record by

Watkins, or in Watkins, that Takahashi or Dangond are the basis for the teaching that HDACi are useful for treating osteoarthritis. Further, Watkins classifies both osteoarthritis and rheumatoid arthritis as inflammatory- not autoimmune- conditions, as Applicant would assert.

(1) Watkins does not provide a specific example wherein an HDAC inhibitor is used to treat osteoarthritis and does not provide an enabling disclosure for such a method of treatment:

As stated in MPEP §2121, "When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980)." Here, Watkins clearly and unambiguously anticipates each and every element- administering an HDACi to treat osteoarthritis and states that HDAC inhibitors (e.g. Trichostatin A) were known to be used in the treatment of conditions including osteoarthritis and RA. In rebuttal, Applicant has not provided facts but merely assertion and conjecture as to the reason Watkins cites Takahashi and Dangond.

With regards to the operability of a reference, MPEP § 2121 further states, "A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)." Additionally, in determining the "knowledge" necessary "to make the claimed invention," the examiner finds guidance in MPEP 2141.03 which states (in part), "**A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton**." *KSR International Co. v.*

Teleflex Inc., 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* At 1396, 82 USPQ2d at 1396. **The "hypothetical person having ordinary skill in the art" to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art**." *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.). (emphasis added).

Here, the public was, indeed, in possession of the invention, as Watkins states- as acknowledged by Applicant in the Appeal Brief, that HDACi are taught by Watkins to treat osteoarthritis, amongst other conditions, albeit Applicant contends it is a non-enabling disclosure. Here, Applicant has provided no evidence that, given the explicit instruction by Watkins that HDACi are used for treating osteoarthritis, and that the Court has held the artisan to be "one of ordinary creativity" who would have "the capability of understanding the scientific …principles applicable to the pertinent art," one would not be in possession of how to treat osteoarthritis with HDACi, given that administration of pharmaceuticals to treat conditions is a notoriously well known and widely practiced technique. Further, in light of *Donahue* (cited by

Applicant throughout the Brief), the artisan would be in possession, as the artisan would be capable of combining the description of Watkins with conventional knowledge of formulation of pharmaceuticals to arrive at the claimed invention. Further, the artisan, when looking at the disclosure of Watkins would be aware that if a compound is used to treat a condition, one would use a therapeutically effective dose, otherwise it would fail to treat the condition.

(2) The references referred to by Watkins in support of the statement that the method of treatment of osteoarthritis using HDACi's was well known do not even mention these conditions and thus do not support the assertion made by Watkins:

As stated above, the rejection is based upon Watkins and was not based upon Takahashi or Dangond. Both references are cited as "see e.g.", in the statement: inflammatory diseases (e.g. osteoarthritis, rheumatoid arthritis) (see e.g. Dangond et al., 1998; Takahashi et al.; 1996). It appears that Applicant's arguments would have one believe that the statement should read: Inflammatory diseases (osteoarthritis- Dangond, rheumatoid arthritis- Takahashi), which is not the case. The rejection is based on Watkins, and there is no explicit statement that Dangond or Takahashi has been cited explicitly for osteoarthritis or rheumatoid arthritis, and thus any assertions that the absence of explicit teachings in Dangond or Takahashi are not germane to the rejection of record.

Additionally, the examiner disagrees with Applicant's assertions as to what these references provide in the way of teachings, in that Watkins does not explicitly present the two cited references as being specific to RA and/or osteoarthritis and as interpreted by the examiner provide fundamental science regarding general cellular inflammation. Absent a specific statement in Watkins that those references are explicitly cited to show treating RA/osteoarthritis

is the reason they are cited, one cannot conclude that was the intent of Watkins. In contrast, the examiner has previously provided sufficient evidence that RA was treatable with HDAC inhibitors (e.g. Kammer; WO 02/055017 A2, PTO 1449, 6/24/05, cited in Office Action 4/20/06).

(3) None of the other references of record indicate that osteoarthritis is "known to be mediated by HDAC" or "known to be treated by HDAC inhibitors" and (4) the Examiner has not pointed to any other references in support of his position that Watkins is enabling for the treatment of osteoarthritis:

Watkins, alone, provides the evidence that it was known to the artisan. Further, in direct contrast to Applicant's assertions that the examiner has not provided any references, the instant disclosure (page 6, 2nd full paragraph) states that HDAC inhibitors have been used for RA and osteoarthritis ("Additionally, in the patent specification (Patent Reference 1) for the FK228 reduced form, a number of diseases are cited for the reason that the FK228 reduced form is effective for diseases induced by abnormal gene expression by its HDAC-inhibitory activity. Therein, although rheumatic arthritis and osteoarthritis are cited, any specific effect is not described and the basis which indicates a therapeutic effect is not shown."). Clearly, Applicant's own specification acknowledges the artisan used HDACi to treat osteoarthritis.

Further, Applicant's own specification admits treating osteoarthritis with hyaluronic acid (an HDACi) was known ("in the current method for treatment") "only as a symptomatic treatment of alleviating pain involved in cartilage degeneration and subchondral bone destruction" (page 7).

In response to Applicant's assertion/requirement that a secondary reference showing it is known is required to show operability, the examiner has provided CHUNG (US 2005/0245439 A1), which also provides that HDACi are/were known to be used in treating osteoarthritis (e.g. claims 1 and 14 of Chung), as discussed above in detail.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANDREW D. KOSAR whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654